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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/386,450	08/31/1999	GERTRUD HOTTEN	P564-9022	1400

7590 11/25/2002

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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/25/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/386,450	HOTTEN ET AL.	
	Examiner	Art Unit	
	David S Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,9,11,13,16,20-22 and 24-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,9,11,13,16,20-22 and 24-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *08/288,508* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed September 20, 2002 (Paper No. 23) has been entered. Claims 6, 9, 11, 13, 16, 20-22, 24-29 are pending and being examined. Any objection and/or rejection of record that is not maintained and/or repeated in this Office action is withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Citations by the examiner are in an alphanumeric format, such as "(a1)", wherein the "a" refers to the reference cited on the Notice of References Cited, PTO-892, and the "1" refers to the Paper No. to which the Notice of References Cited, PTO-892, is attached.

Maintained Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 102

Claims 11, 27 are rejected under 35 U.S.C. 102(e) as being anticipated by Lee (1, cited by Applicants). Applicants argue that claim 11 has been amended such that the Lee sequence is not comprised. Applicants arguments have been fully considered but they are not persuasive. The claims do not distinguish over Lee. The claims are directed to a protein of the TGF-β family encoded by a DNA molecule which comprises a part of SEQ ID NO: 1 which encodes the amino acid sequence according to SEQ ID NO: 13. As noted in the last Office action, amino acids 394 to 495 of Lee's GDF-5 are identical to the amino acid sequence of the present application's SEQ ID NO: 13. Accordingly, Lee discloses a protein of the TGF-β family encoded by a DNA molecule which comprises a part of SEQ ID NO: 1 which encodes the amino acid sequence according to SEQ ID NO: 13.

Claim Rejections - 35 USC § 103

Claims 9, 11, 13, 16, 20, 24-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee (1, cited by Applicants) as applied to claim 11 above and further in view of Oppermann (2, cited by Applicants).

The rejection of record is applied to claim 28, because Lee teaches a protein of the TGF-β family encoded by a DNA molecule which comprises a nucleotide sequence which encodes a portion of the amino acid sequence according to SEQ ID NO: 2, wherein said portion comprises the seven cysteine as shown in SEQ ID NO: 13.

Applicants argue that claim 11 has been amended such that the Lee sequence is not comprised. Applicants arguments have been fully considered but they are not persuasive. The protein in the claimed compositions is indistinguishable from Lee's polypeptide.

Applicants argue that neither Lee or Oppermann protect the angiogenesis. Applicants arguments have been fully considered but they are not persuasive. The intended uses of the claimed invention and/or pharmaceutical compositions do not result in a structural difference between the present invention and the prior art pharmaceutical compositions and do not patentably distinguish the claimed invention from the prior art. The invention is prima facie obvious over the prior art.

Double Patenting

Claims 6, 9, 11, 13, 16, 20-22, 24-29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6120760.

If necessary, claims 6, 9, 11, 13, 16, 20-22, 24-29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6120760 in view of Lee (1, cited by Applicants) and further in view of Oppermann (2, cited by Applicants).

Applicants argue that Hotten (U.S. Patent No. 6120760) was filed after U.S. patent application 08288508 was filed, the present application is a divisional of 08288508, and therefore Hotten (U.S. Patent No. 6120760) should not be prior art. Applicants arguments have been fully considered but they are not persuasive. A double patenting rejection of the obviousness-type is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103" except that the patent principally underlying the double patenting rejection is not considered prior art (MPEP § 804.II.B.1.). The issue of Hotten (U.S. Patent No. 6120760) not being prior art is not relevant to the present rejection.

New formal matters, objections, and/or rejections:

Claim Rejections - 35 USC § 112

The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28 is indefinite over the recitation of "comprises the seven cysteine as shown in SEQ ID NO: 13" because it is unclear if the protein comprises seven cysteines or comprises the seven cysteine domain of SEQ ID NO: 13. The metes and bounds are not clearly set forth.

Claim 16 is indefinite because it recites the term "dental implant". Because the instant specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of "dental implant" an artisan cannot determine what additional or material limitations are placed upon a claim by the presence of this element. The metes and bounds are not clearly set forth.

Claims 24, 28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Although the present application discloses "application in connection with angiogenesis" (page 10, full paragraph 1), the present application does not describe "application in cases where angiogenesis is advantageous or desired". The introduction of such a limitation changes the meaning, scope, and content of the original disclosure and raises the issue of new matter.

Claims 9, 11, 13, 16, 20, 24-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Although the present application shows a comparison between the amino acid sequence of MP-52 and several members of the BMP protein family starting with the first of the seven conserved cysteine residues (SEQ ID NO: 13) (Figure 1), the present application does not describe or contemplate an isolated protein that is

SEQ ID NO: 13. The introduction of such a limitation changes the meaning, scope, and content of the original disclosure and raises the issue of new matter.

Claim Rejections - 35 USC § 102

Claims 24, 28 are rejected under 35 U.S.C. 102(b) as anticipated by Hotten (v24) as evidenced by Hotten (w24) and Yamashita (u24).

Although the present application discloses "application in connection with angiogenesis" (page 10, full paragraph 1), the present application does not describe "application in cases where angiogenesis is advantageous or desired". The introduction of such a limitation changes the meaning, scope, and content of the original disclosure and raises the issue of new matter. The claims are not entitled to the benefit of Applicants' earlier applications filing dates.

Hotten (v24) teaches ectopic cartilage and bone formation in rodents administered huGDF-5 (paragraph bridging pages 68 and 70). The huGDF-5 was expressed as previously described by Hotten (w24). See Hotten (v24) at page 66, left column, full paragraph 2. The amino acid sequence of huGDF-5 as disclosed by Hotten (w24) is identical to the present application's SEQ ID NO: 2, as indicated below:

```
ENTRY            JC2347     #type complete
TITLE            growth/differentiation factor 5 - human
ORGANISM         #formal_name Homo sapiens #common_name man
DATE             20-Feb-1995 #sequence_revision 20-Feb-1995 #text_change
                   28-May-1999
ACCESSIONS       JC2347
REFERENCE        JC2347
   #authors      Hoetten, G.; Neidhardt, H.; Jacobowsky, B.; Pohl, J.
   #journal      Biochem. Biophys. Res. Commun. (1994) 204:646-652
   #title        Cloning and expression of recombinant human
                   growth/differentiation factor 5.
   #cross-references MUID:95071375
   #accession    JC2347
      ##molecule_type DNA
      ##residues      1-501 ##label HOE
      ##cross-references GB:X80915; NID:g671524; PIDN:CAA56874.1; PID:g671525
GENETICS
   #gene         GDB:BMP9
      ##cross-references GDB:433948
   #introns      211/1
KEYWORDS         glycoprotein
FEATURE
   189               #binding_site carbohydrate (Asn) (covalent) #status
                       predicted\
   381-382           #cleavage_site Arg-Ala (unidentified proteinase) #status
```

```
                    predicted
SUMMARY         #length 501  #molecular-weight 55410  #checksum 5334

  Query Match          100.0%;  Score 3662;  DB 2;  Length 501;
  Best Local Similarity 100.0%;  Pred. No. 0.00e+00;
  Matches   501;  Conservative    0;  Mismatches   0;  Indels   0;  Gaps   0;

Db      1 MRLPKLLTFLLWYLAWLDLEFICTVLGAPDLGQRPQGTRPGLAKAEAKERPPLARNVFRP 60
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy      1 MRLPKLLTFLLWYLAWLDLEFICTVLGAPDLGQRPQGTRPGLAKAEAKERPPLARNVFRP 60

Db     61 GGHSYGGGATNANARAKGGTGQTGGLTQPKKDEPKKLPPRPGGPEPKPGHPPQTRQATAR 120
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy     61 GGHSYGGGATNANARAKGGTGQTGGLTQPKKDEPKKLPPRPGGPEPKPGHPPQTRQATAR 120

Db    121 TVTPKGQLPGGKAPPKAGSVPSSFLLKKAREPGPPREPKEPFRPPPITPHEYMLSLYRTL 180
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy    121 TVTPKGQLPGGKAPPKAGSVPSSFLLKKAREPGPPREPKEPFRPPPITPHEYMLSLYRTL 180

Db    181 SDADRKGGNSSVKLEAGLANTITSFIDKGQDDRGPVVRKQRYVFDISALEKDGLLGAELR 240
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy    181 SDADRKGGNSSVKLEAGLANTITSFIDKGQDDRGPVVRKQRYVFDISALEKDGLLGAELR 240

Db    241 ILRKKPSDTAKPAAPGGGRAAQLKLSSCPSGRQPASLLDVRSVPGLDGSGWEVFDIWKLF 300
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy    241 ILRKKPSDTAKPAAPGGGRAAQLKLSSCPSGRQPASLLDVRSVPGLDGSGWEVFDIWKLF 300

Db    301 RNFKNSAQLCLELEAWERGRAVDLRGLGFDRAARQVHEKALFLVFGRTKKRDLFFNEIKA 360
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy    301 RNFKNSAQLCLELEAWERGRAVDLRGLGFDRAARQVHEKALFLVFGRTKKRDLFFNEIKA 360

Db    361 RSGQDDKTVYEYLFSQRRKRRAPLATRQGKRPSKNLKARCSRKALHVNFKDMGWDDWIIA 420
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy    361 RSGQDDKTVYEYLFSQRRKRRAPLATRQGKRPSKNLKARCSRKALHVNFKDMGWDDWIIA 420

Db    421 PLEYEAFHCEGLCEFPLRSHLEPTNHAVIQTLMNSMDPESTPPTCCVPTRLSPISILFID 480
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy    421 PLEYEAFHCEGLCEFPLRSHLEPTNHAVIQTLMNSMDPESTPPTCCVPTRLSPISILFID 480

Db    481 SANNVVYKQYEDMVVESCGCR 501
          |||||||||||||||||||||
Qy    481 SANNVVYKQYEDMVVESCGCR 501.
```

The majority of the huGDF-5 expressed by Hotten (v24) consisted of 121 amino acids beginning at Arginine[381]. See Hotten (v24) at page 68, paragraph bridging left and right columns. These 121 amino acids comprise the mature portion of the present application's SEQ ID NO: 2 and comprises the present application's SEQ ID NO: 13. The huGDF-5 was administered in a composition comprising bone matrix or collagen solution. See Hotten (v24) at page 67, right column, full paragraphs 1-2. Yamashita teaches that angiogenesis is involved in the bone formation process (Abstract). Accordingly, Hotten (v24) teaches a pharmaceutical composition for application in cases where angiogenesis is advantageous or desired. The intended uses or suitability of the claimed invention and/or pharmaceutical compositions do not result in a structural difference between the present invention and the prior art pharmaceutical compositions and do not patentably distinguish the claimed invention from the prior art.

Claim Rejections - 35 USC § 103

Claims 9, 11, 13, 16, 20, 24-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Celeste (a24).

Although the present application shows a comparison between the amino acid sequence of MP-52 and several members of the BMP protein family starting with the first of the seven conserved cysteine residues (SEQ ID NO: 13) (Figure 1), the present application does not describe or contemplate an isolated protein that is SEQ ID NO: 13. The introduction of such a limitation changes the meaning, scope, and content of the original disclosure and raises the issue of new matter. The claims are not entitled to the benefit of Applicants' earlier applications filing dates.

Celeste teaches purified human MP52 proteins which contain the amino acid sequence represented by amino acids #1 to #120 of SEQ ID NO:4. It is also expected that the amino acid sequence from amino acids #17 or #19 to #119 or #120 of SEQ ID NO:4 will retain activity. Thus, the DNA sequence from nucleotides #845, #893 or #899 to #1201 or #1204 are expected to encode active proteins. See column 7, full paragraph 2. Amino acids 19 to 120 of Celeste's SEQ ID NO: 4 are identical to SEQ ID NO: 13, as indicated below:

```
US-08-333-576C-4
; Sequence 4, Application US/08333576C
; Patent No. 6027919
;  INFORMATION FOR SEQ ID NO:  4:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  120 amino acids
;      TYPE:  amino acid
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  protein
US-08-333-576C-4

  Query Match           100.0%;  Score 568;  DB 3;  Length 120;
  Best Local Similarity  100.0%;  Pred. No. 1.2e-54;
  Matches  102;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy      1 CSRKALHVNFKDMGWDDWIIAPLEYEAFHCEGLCEFPLRSHLEPTNHAVIQTLMNSMDPE 60
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     19 CSRKALHVNFKDMGWDDWIIAPLEYEAFHCEGLCEFPLRSHLEPTNHAVIQTLMNSMDPE 78

Qy     61 STPPTCCVPTRLSPISILFIDSANNVVYKQYEDMVVESCGCR 102
          |||||||||||||||||||||||||||||||||||||||||||
Db     79 STPPTCCVPTRLSPISILFIDSANNVVYKQYEDMVVESCGCR 120.
```

Celeste teaches a pharmaceutical composition comprising MP52 (column 11, full paragraph 2) and biocompatible, porous matrix materials that can be biologically degraded, wherein the protein is contained on and/or in a natural of synthetically prepared matrix material (column 12, line 40, through column 13, line 22). Celeste does not teach an isolated protein consisting of amino acids 19 to 120 of Celeste's SEQ ID NO: 4. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make an isolated protein consisting of amino acids 19 to 120 of Celeste's SEQ ID NO: 4 and a pharmaceutical composition comprising same and biocompatible, porous matrix materials that can be biologically degraded, wherein the protein is contained on and/or in a natural of synthetically prepared matrix material, with a reasonable expectation of success. One of ordinary skill in the art would motivated to make this modification because it is also expected that the amino acid sequence from amino acids #19 to #120 of Celeste's SEQ ID NO:4 will retain activity. The intended uses or suitability of the claimed invention and/or pharmaceutical compositions do not result in a structural difference between the present invention and the prior art pharmaceutical compositions and do not patentably distinguish the claimed invention from the prior art. The invention is prima facie obvious over the prior art.

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (703) 305-4050. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M.

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IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHTFAX NUMBERS:

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ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
NOVEMBER 24, 2002